Cochlear Implantation in Individuals with Usher Syndrome

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International Symposium on USH 2014

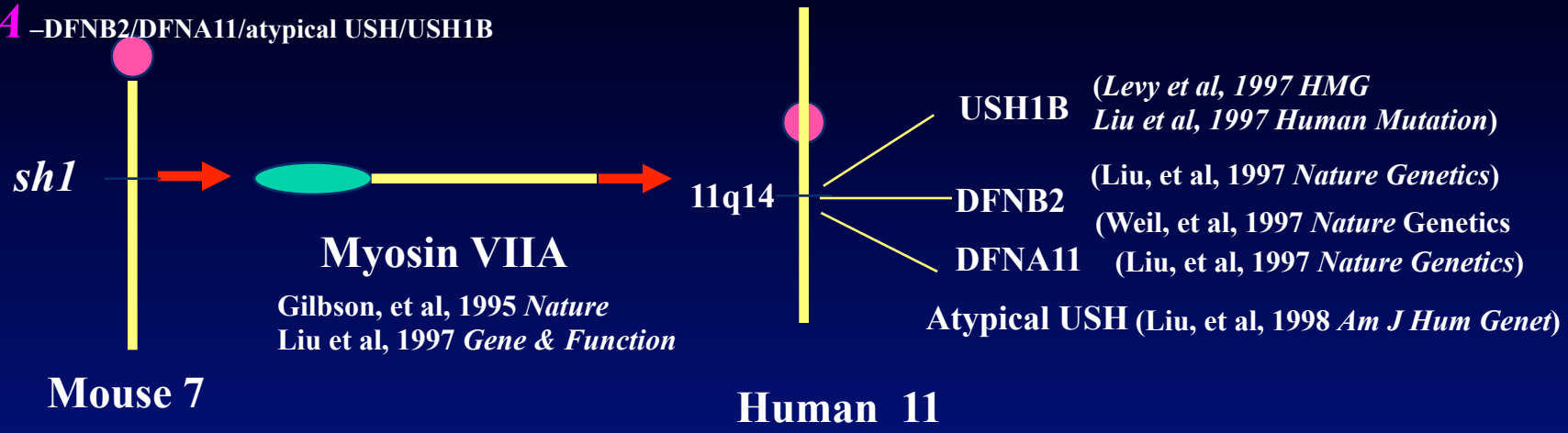
My Diversified Education Journey as a Physician Scientist

Degree	Year	Major	Supports	University
M.D. China	9/1979-7/1987	Medicine		West China Univ. of Med Sci (WCUMS),
Ph.D.	7/1991-7/1995	Human Genetics.	RIND	University of Manchester, Manchester, UK
Post-Doc	8/1995-10/1998	Molecular Genetics	RIND/MRC	Mammalian Genetic Unit, Oxford, UK
Internship	6/2003-6/2004	General Surgery	FFB/DRF/NIH	Jackson Memory Hospital/ University Miami, USA
Residency	7/2004-6/2008	Otolaryngology (ENT)	NIH	Jackson Memory Hospital/ University Miami, USA

Usher genes in non-syndromic deafness & USH

Steven Brown/Karen Steel, Walter Nance, Christine Petit, Maria Bitner-Glindzicz, Tom Friedman, *Sam Jacobson,* J Fielding Hejtmancik *Ken Johnson, Zheng –Yi Chen*

MYO7A **–DFNB2/DFNA11/atypical USH/USH1B**



USH1C **– USH1/DFNB18**
Verpy et al, *Nature Genetics* 2000
Bitner-Glindzicz et al, *Nature Genetics* 2000

Ouyang et al, Liu DFNB18 without RP *Human Genetics* 2002
Ouyang et al, Liu, *Clinical Genetics*, 2003

USH1C– DOCK4 and KO mouse model: Yan et al Liu JMB 2006; Tian et al, Brain Research 2010

CDH23 **– USH1D Bork et al, 2001 *AJHG* - USH1D/CDH23 identification; Ouyang et al Liu (2005)** Schutley et al, *JMG* 2011

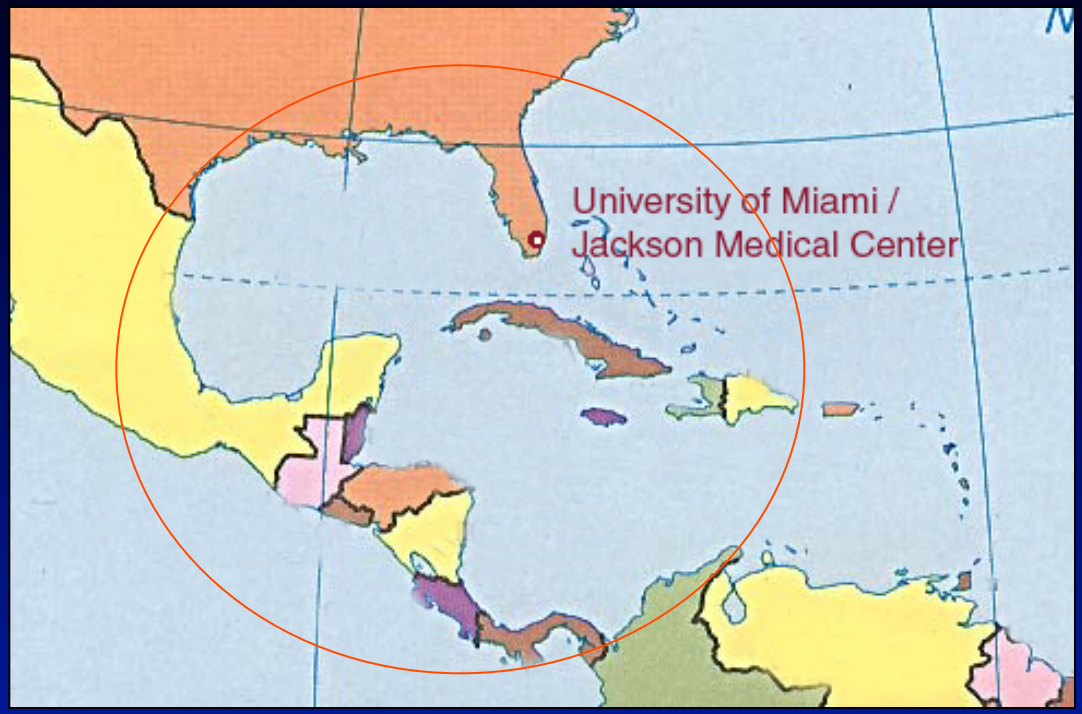
Whirler **–USH2D/DFNB31** Mburu, P., et al (2003) ***Nature Genetics*** 34(4):421-8.

CDH23 and PCDH15 - Evidence for hearing loss caused by an interaction of both gene mutations in digenic heterozygotes in both mice and humans Zheng et al, Liu *Human Molecular Genetics* 2005

USH2A **– USH2A: Liu et al, AJHG 1999; Dreyer et al, AJHG 2001;** Schwarts et al, ***Invest Ophthalmol Vis Sci.*** (2005); Jacobson et al, HMG 2010

USH3 - Herrera et al, ***Invest Ophthalmol Vis Sci.*** (2008)

Teaching Hospitals - over *2,500* Beds and over 100,000 Emergency Room Visits Annually



Jackson Memorial

UMHC/Sylvester Cancer Center

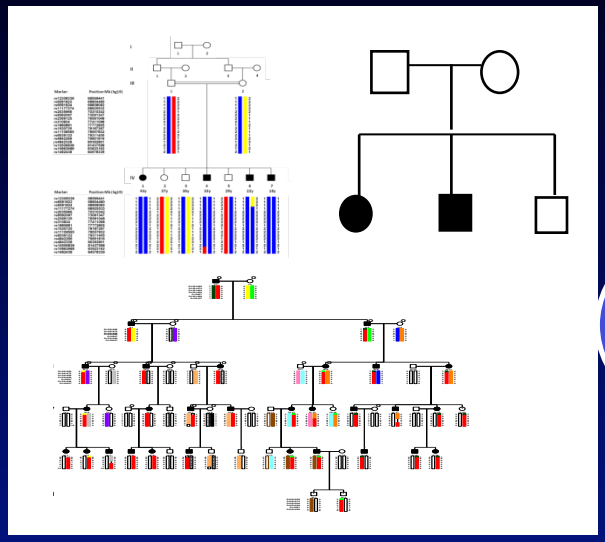
Anne Bates Leach Hospital

University of Miami Hospital

Veterans Administration

Miami Otogenetic Program

Multidisciplinary collaboration effort



Gene Identification

DNA sample collection, population-based cohort data, gene mapping, MiamiOtoGenes, & whole exome sequencing

Clinical Management & Diagnosis

diagnosis, counseling, personalized sequence profile

Interventions

Gene Function/Therapeutic

In vitro and *in vivo* structural and functional studies

Gene/cell/drug-based studies

All projects in the program are currently supported by 6 NIH R01 grants and UM funds

UHealth UNIVERSITY OF MIAMI HEALTH SYSTEM | UNIVERSITY OF MIAMI MILLER SCHOOL of MEDICINE

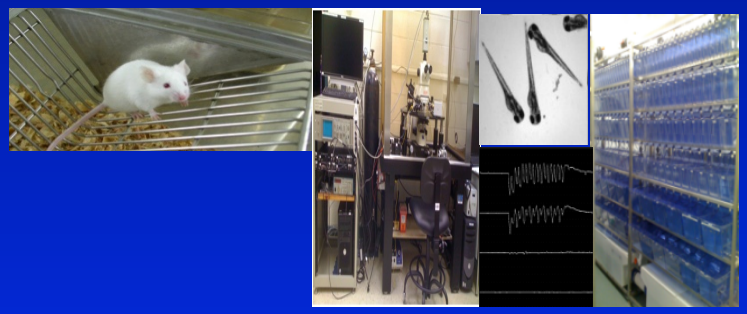
Miami Otogenetic Program

Miami Molecular Otogenetic Program

HIGG

Molecular Genetic Lab

Gene Function Lab

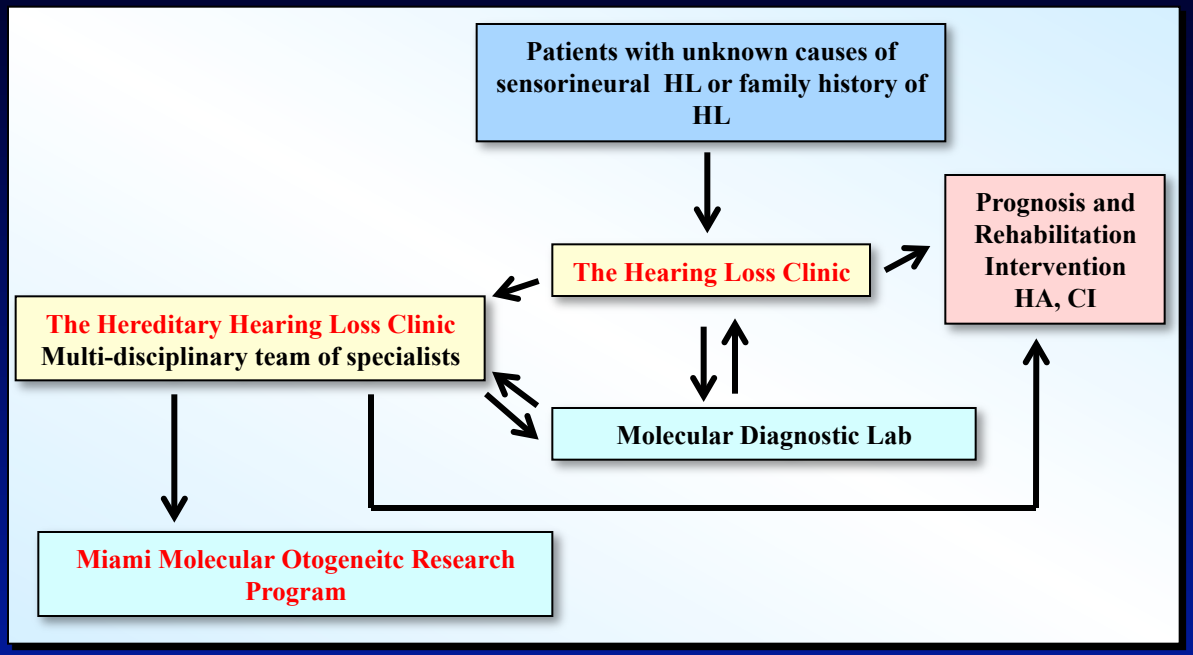


Miami Clinic Otogenetic Program

The Miami Hearing Loss Clinic

The Miami Hereditary Hearing Loss Clinic

Miami Clinical Otogenetic Program



The Miami Hearing Loss Clinic

The Miami Hereditary Hearing Loss Clinic

BPEI

Miami Ear Institute

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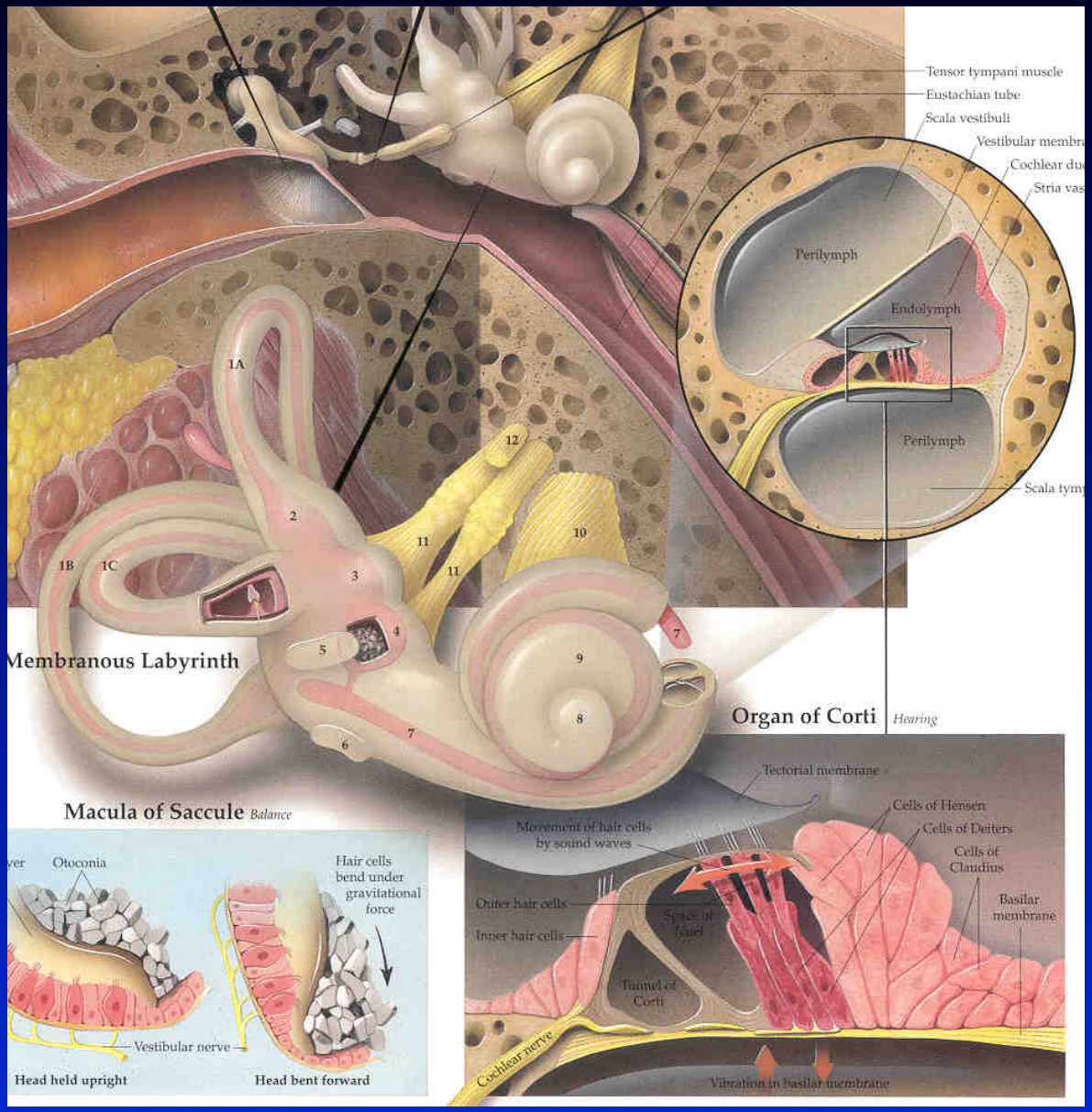
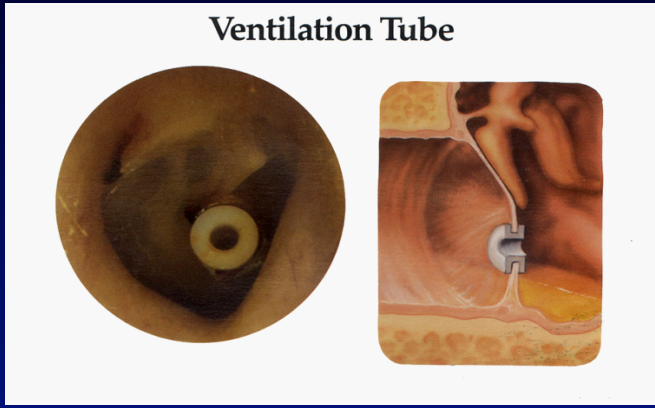
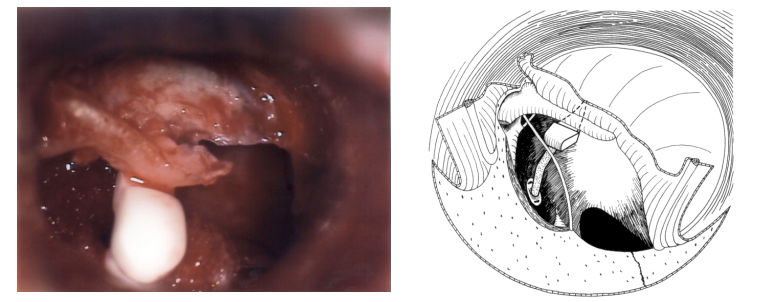
The Anatomy of Mammalian Ear



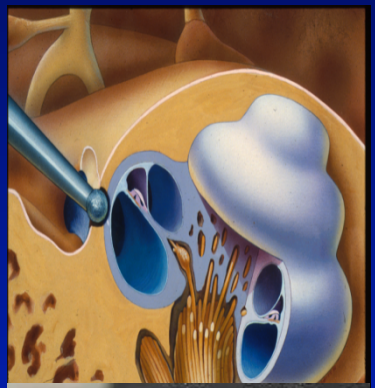
- **Helen Keller claimed that "To be deaf is a greater affliction than to be blind".**
- **The most common human sensory disorder**
- **At least 2 per 1,000 infants at birth**
- USH 0.6-28% of individuals with deafness

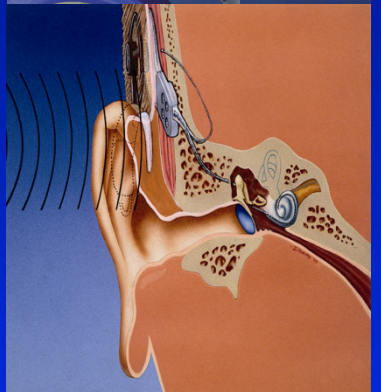
Surgery for Conductive Hearing Loss





Hearing Rehabilitations for Sensorineural Hearing Loss

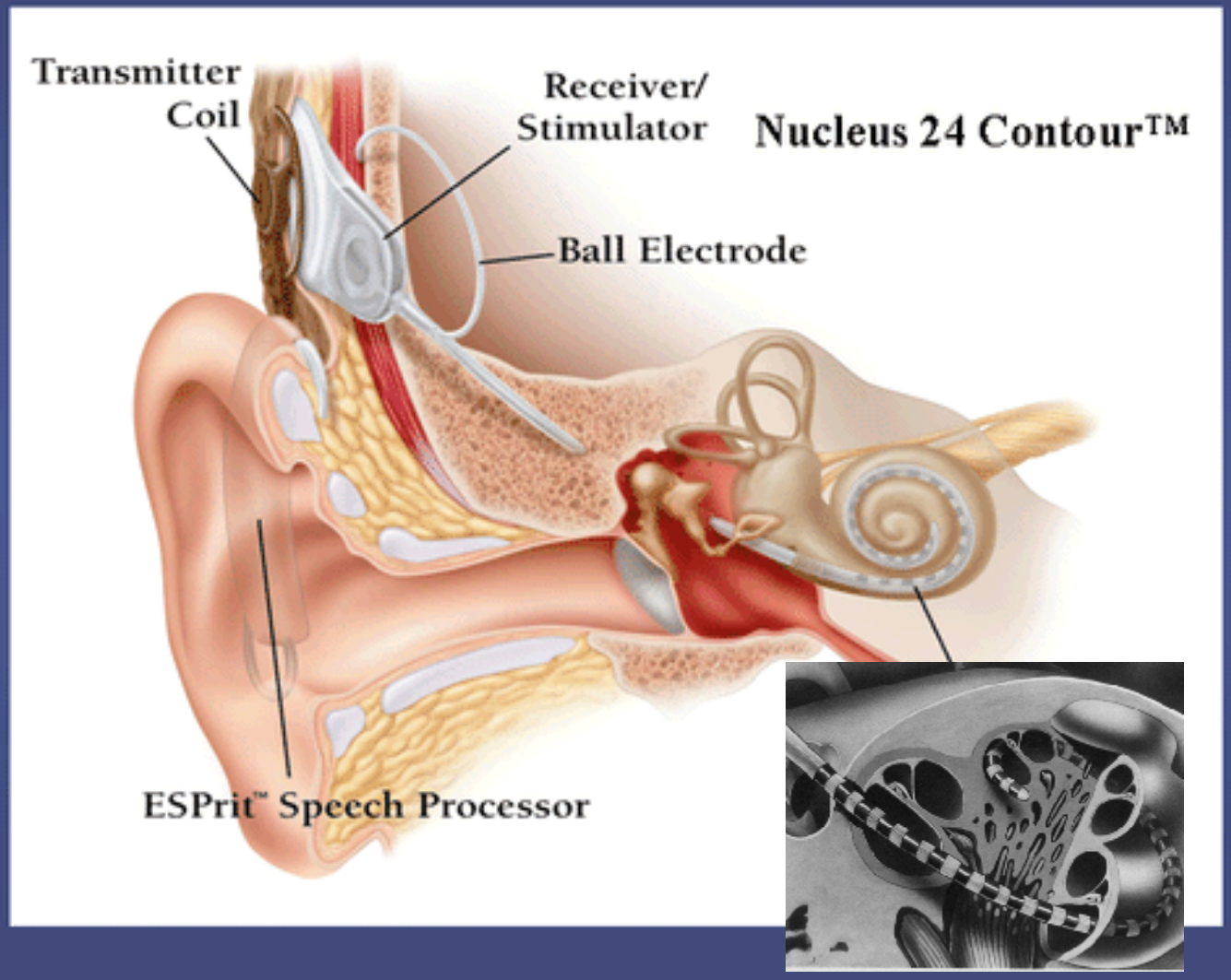




History

- Cochlear implants as we know them now are the result of intensive research over the last five decades.
- However, there is a long history of attempts to provide hearing by the electrical stimulation of the auditory system.
- The centuries old interest in the biologic application of electricity was the basis for the development of cochlear implants.
- Lasker Award 2013 to three CI people

Anatomy of a Cochlear Implant

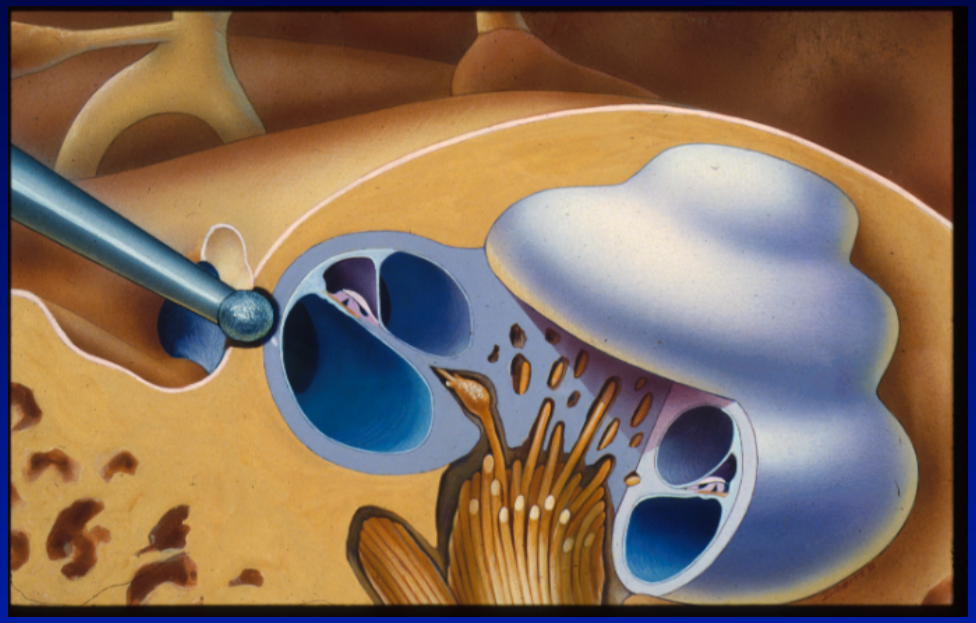


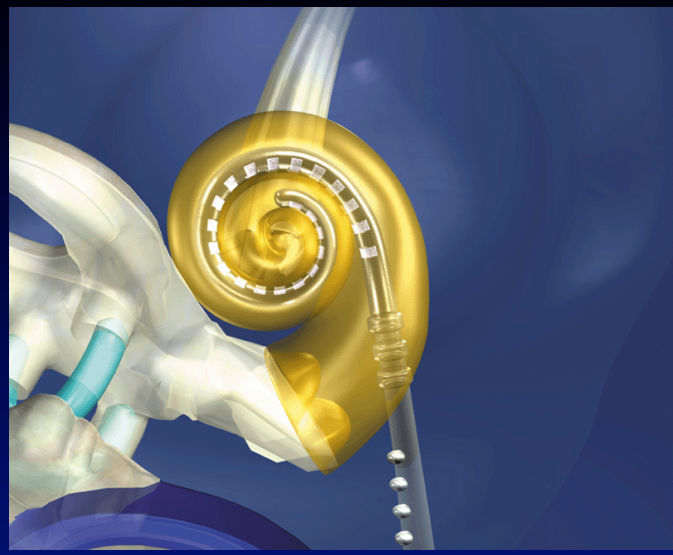
Hardware

- Currently, there are three major corporations manufacturing cochlear implants for use in the United States

The Electrode Array

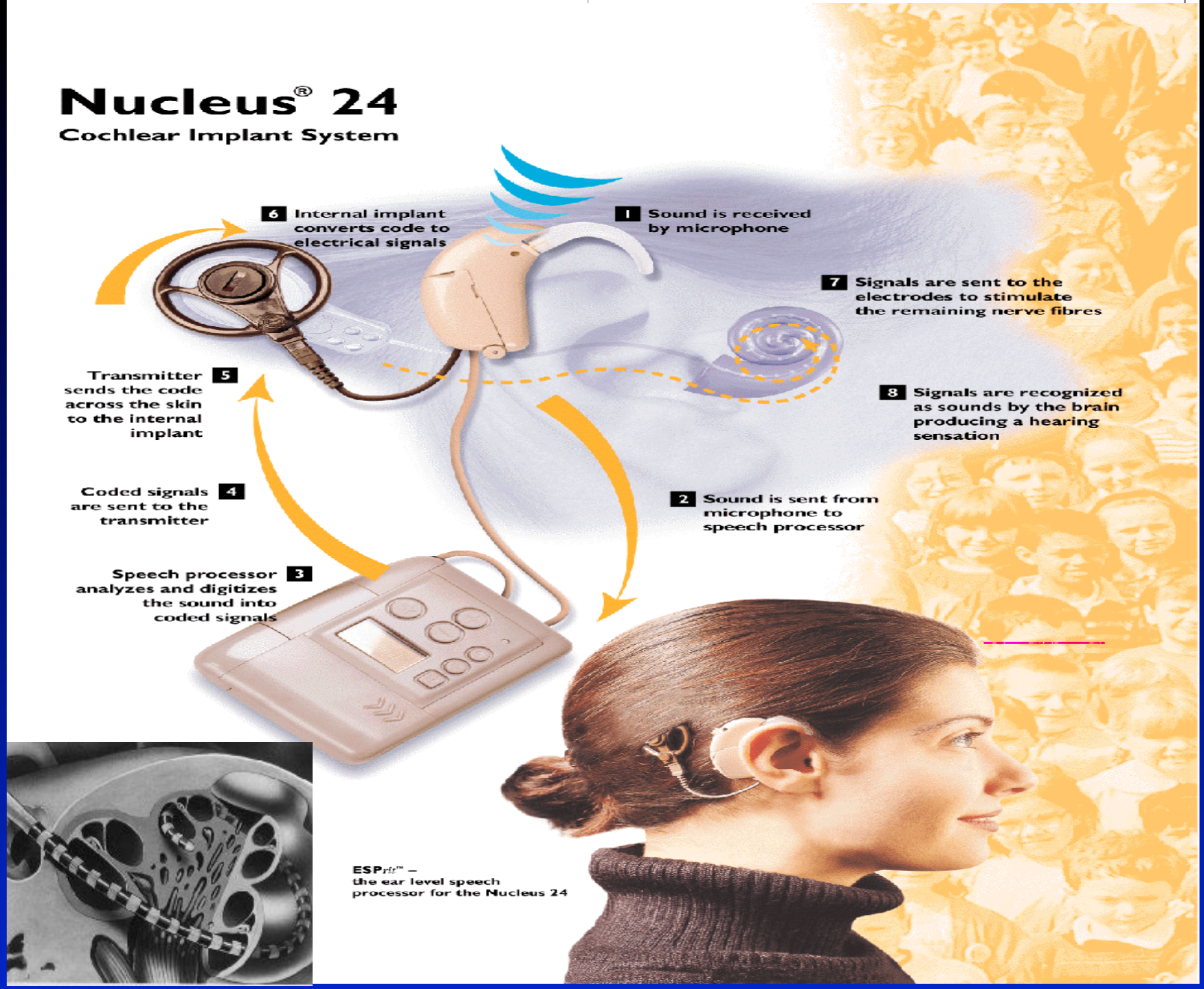
- Nucleus 24 Contour electrode
- 22 electrode half bands spaced logrithmically through the cochlea
- Insertion depth 1½ turns of the cochlea





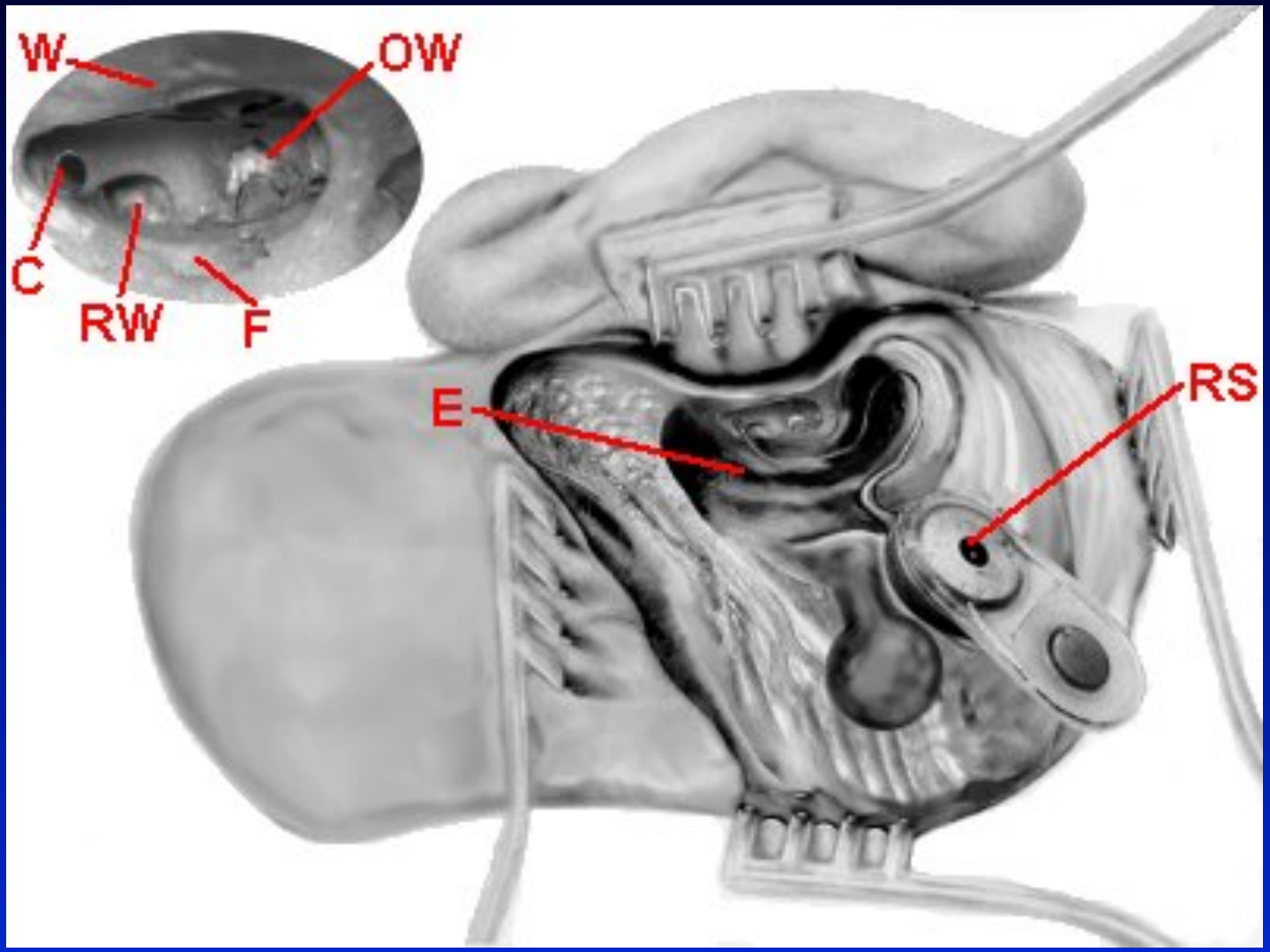
COCHLEAR IMPLANT

Cochlear implant. Electronic devices that substitute the function of damaged hair cells by providing sound information as coded electrical signal to the remaining nerve fibers.



•Microphone – Processor/MAP – Coil – Receiver/Stimulator - Electrode

Surgical Technique



Language is the ultimate goal of cochlear implantation in children

- Svirsky, Miyamoto, et al (2000)
  - Rate of language development was higher for CI children than for unimplanted deaf children

- Favorable factors:
  - Implantation at early age
  - Duration of CI use
  - Good hearing perception
  - Oral communication

Diagnosis of Usher Syndrome

Rationale for Deafness Gene Testing

- Early detection is important for successful speech outcomes and possible intervention with cochlear implantation
- Clinical diagnosis is not always straightforward in young patients
- Genetic testing has been investigated as an alternative for early identification, identifying the genetic nature of "sporadic cases", and maintaining cost efficiency
- Establishment of high-throughput techniques (NGS) should soon provide comprehensive testing covering all genes
- Early confirmation (or exclusion) would help predict whether retinal degeneration can be expected in addition to congenital hearing impairment

Herman and Liu, 2010 in Satpal Ahuja (Sweden), editor: ***Usher syndrome: Pathogenesis, Diagnosis and Therapy***

Treatment of Usher Syndrome

- There are differences in auditory performance that are not attributable to age at implantation or auditory training
- In Usher genes, cochlear nerve and spiral ganglion cells are preserved and this suggests the potential for excellent performance
- Virtually all members of the deaf community view the visual impairment as a devastating handicap
- **Swift deterioration of vision makes sign language only a temporary solution, emphasizing the importance of cochlear implantation in USH1 syndrome**
- **Age appears to be the most critical prognostic factor in cochlear implantation of Usher syndrome, with the best speech results in Usher syndrome obtained in patients who undergo cochlear implantation at an earlier age**

Vivero; Kenneth Fan; Simon Angeli; Thomas J Balkany, and **Liu XZ** (2010) Cochlear Implantation in Common Forms of Genetic Deafness (review) ***Int J of Ped Otol* 2010** 74, 1107-12

Treatment of Usher Syndrome

- USH2 and 3 may have variable residual hearing
- USH1 will likely only have low frequency residual hearing present at 90-100 dB
- USH1 patients derive little benefit from amplification and routinely are offered cochlear implantation
- If patient/family does not elect for CI, audioverbal therapy and/or sign language
- USH2 and many USH3 amenable to hearing amplification, so HAs are fitted as a first step, although some go on to receive CIs

CIs in Usher Syndrome

*Liu XZ,, et al. Cochlear implantation in individuals with usher type 1 syndrome. *Int J Pediatr Otorhinolaryngo*l. 2008;72(6):841-847.

- Nine USH1 patients with congenital deafness, positive electroretinography, vestibular dysfunction, and inability to benefit from conventional amplification were implanted
- Ages 2 to15 (mean of 5.4 years)
- Children implanted before 3 years of age showed the greatest improvement in both open-set and closed-set scores
- Four children implanted before 3 years of age: three had closed-set monosyllable recognition of 76%, two had 80% open set word recognition with lip reading, and one patient had 60% open-set recognition without lip reading
- After 6 years of age, mean closed-set scores were 54%, and only one patient had 82% open-set word recognition with lip reading
- No association between preoperative mode of communication and postoperative speech perception

Case Presentation

- 43yo woman with Usher Type II
- Blind, uses seeing eye dog
- Previously able to communicate with HA's
- Experienced SSNHL AS 5/08
- AS was better hearing ear
- No improvement with IT Dex x 2
- CI AS 9/08
- CI AD 12/08
- Audiogram 6/09 showed
  - AS SRT 25dB, HINT 91%, CNC 70%
  - AD SRT 35, HINT 87%

Case Presentation

- 10 y/o boy with congenital profound HL
- CI when 3 y/o, but outcome was poor
- Dx as USH1B with *MYO7A* mutations in 2010
- Dx autism in 2010
- Using implant more for environment contact and preparing worsening eye-sight deteriorates

Conclusions

- An appropriate management algorithm facilitates effective patient care
- Early detection of Usher syndrome is important for successful speech outcomes
- Dual sensory nature of USH emphasizes the importance of CI, since usefulness of sign language will decrease with increasing vision loss
- CI has been shown to be an effective treatment of severe hearing loss, especially in young patients with USH1
- Team will need to become increasingly familiar with available tests and their interpretation in order to use them effectively and counsel patients regarding prognosis and treatment